REMARKS

Claims 1-25 are pending in this application. Claims 18-21 have been withdrawn from consideration as being drawn to a non-elected invention. Claims 1, 6, 16, 17, 22 and 23 have been amended. Claims 24-25 have been newly added.

New claim 24 recites that the "method does not utilize the dead-end elimination algorithm to eliminate rotamers that are mathematically provable to be inconsistent with a global minimum energy solution of a system." Support for new claim 24 appears in the specification at page 4, lines 1-4, which discusses prior art methods including the dead-end elimination algorithm. Page 3 of the specification states that "*de novo* design of stable and unique proteins, remains a challenging problem."

New claim 25 corresponds to amended claim 1, except that new claim 24 recites the transition language "consisting of." Support for new claim 24 appears throughout the specification and claims as originally filed. No new matter has been added.

Applicants, by amending any claims, make no admission as to the validity of any rejection made by the Examiner against any of these claims. Applicants reserve the right to reassert the original claim scope of any claim amended herein, in a continuing application.

Claim 1 has been amended to recite "A computer-implemented method for predicting at least one amino acid sequence that folds into a specified three-dimensional (3D) structure of a predetermined reference protein or peptide, the at least one amino acid sequence having a biological activity the same as a biological activity of the reference protein or peptide; which method comprises the steps of: a) providing a coordinate set representing the backbone of said 3D structure; b) constructing a reduced virtual

representation for the 3D structure provided in step (a), wherein in said reduced representation, each amino acid has a backbone portion and a side chain portion, the backbone portion of each amino acid being represented by a single sphere and the side chain of each amino acid being represented by one to three additional spheres; c) determining for each amino acid position along the virtual structure representation provided in step (b) its solvent accessibility; d) constructing an initial amino acid sequence by assigning for each amino acid position along the structure an amino acid residue selected randomly from a predefined group of amino acids having a solvent accessibility compatible with the solvent accessibility of said position; e) randomly selecting one or more positions along the sequence provided in step (d) and applying on each position a Monte-Carlo simulation in sequence space and rotamer space, said simulation comprising one or more scoring function calculating steps which include: i) randomly selecting one or more amino acid residues of the same solvent accessibility as that defined for said position to obtain a mutation; ii) for each of the one or more selected positions, calculating an energy difference delta E, between the amino acid residue at the position in the predetermined protein or peptide and each of the one or more selected amino acid residues provided in step (i) based on its said reduced virtual representation; iii) selecting a rotamer having a minimal delta E, or when more than one amino acid are manipulated simultaneously, selecting a rotamer combination having a minimal delta E; iv) accepting the mutation with the rotamer or rotamer combination selected in step (iii) if delta E<0; and v) assigning the amino acid residue or residues and their respective selected rotamer or rotamer combinations selected in step (iii) to said position(s) and moving to another position along the sequence; wherein said simulation steps are repeated until for each position along said sequence, the residue

sequence, the residue and residue's rotamer with the lowest energy score is selected, to obtain a virtually represented amino acid sequence with the lowest total energy score; f) expanding the reduced representation of the virtually represented amino acid sequence obtained in step (e) to its corresponding all-atom sequence representation thereby obtaining an amino acid sequence compatible with the structure of the predetermined protein or peptide; and g) creating a computer output of the expanded all-atom representation of the primary structure(s) obtained in step (f). Support for amended claim 1 can be found throughout the specification and claims as originally filed. No new matter has been added.

Claim 6 has been amended to replace the phrase "is substantially water" with the phrase "is an aqueous solvent." Support for amended claim 6 appears throughout the specification and claims as originally filed. No new matter has been added.

Claim 16 has been amended to recite "the structure of the predetermined protein or peptide" in place of "the predefined 3D structure." Support for amended claim 16 appears throughout the specification and claims as originally filed. No new matter has been added.

Claims 17 and 22 have been amended to correct a minor grammatical error, and to recite "a" in place of "the." Support for amended claims 17 and 22 appears throughout the specification and claims as originally filed. No new matter has been added.

Claim 23 has been amended to replace the phrase "said processing means" with the phrase "said processor." Support for amended claim 23 appears throughout the specification and claims as originally filed. No new matter has been added.

In view of the remarks set forth below, further and favorable consideration is respectfully requested.

I. A page 2 of the Official Action, claims 1 and 17 have been objected to.

The Examiner notes that in claim 1 the word "provide" should be "provided," that "position/s" should be "position(s)," and that "structure/s" should be "structure(s)." With regard to claim 17, the Examiner asserts that the tense of the word "stabilized" should be "stabilizes."

In view of the following, this rejection is respectfully traversed.

Claims 1 and 17 have been amended as suggested by the Examiner. Accordingly, the Examiner is respectfully requested to withdraw this objection.

II. At page 3 of the Official Action, claims 1-17, 22, and 23 have been rejected under 35 USC § 112, second paragraph as being indefinite.

The Examiner asserts that in claim 1, step e) ii), it is unclear as to what is being calculated. With regard to step f) and claim 16, the Examiner asserts that there is insufficient antecedent basis for the limitation "the predefined 3D structure." The Examiner asserts that the term "essentially" is not defined, and that the term "substantially water" is a relative term. With regard to claim 22, the Examiner asserts that the limitation "the native amino acid sequence" lacks sufficient antecedent basis. Lastly, the Examiner asserts that the term "said processing means" in step f) of claim 23, lacks sufficient antecedent basis.

In view of the following, this rejection is respectfully traversed.

Claim 1, step e) ii) has been amended to recite "for each of the one or more selected positions, calculating an energy difference delta E, between the amino acid residue at the position in the predetermined protein or peptide and each of the one or more selected amino acid residues provided in step (i) based on its said reduced virtual

representation." Applicants submit that claim 1, step e) ii) clearly defines what is being calculated. In addition, claim 1 has been amended to delete the term "essentially."

Claim 6 has been amended to replace the term "substantially water" with the term "aqueous solvent."

Claims 17 and 22 have been amended to replace the phrase "the native amino acid sequence" with the phrase "a native amino acid sequence."

Claim 23 has been amended to replace the term "said processing means" with the term "said processor."

In view of the foregoing, it is submitted that claims 1-17, 22 and 23 are clear and definite within the meaning of 35 USC §112, second paragraph. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

III. At page 5 of the Official Action, claims 1-17, 22, and 23 have been rejected under 35 USC § 101, as being directed to non-statutory subject matter.

The Examiner asserts that the instant claims are drawn to a method of predicting at least one amino acid sequence and that the last step, g), is an optional step and as such, is not given patentable weight.

In view of the following, this rejection is respectfully traversed.

Claim 1 has been amended to delete the term "optionally." Accordingly, step g) is a required step and as such, is entitled to patentable weight.

In view of the foregoing, Applicants submit that the presently claimed subject matter is directed to statutory subject matter within the meaning of 35 USC § 101. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

III. At pages 6-10 of the Official Action, claims 1-5, 9-17, 22 and 23 have been rejected under 35 USC § 103 as being unpatentable over Dahiyat et al., and further in view of Herzyk et al. Claims 6-8 have been rejected as being unpatentable over Dahiyat et al., and further in view of Herzyk et al. and further in view of Hurley et al.

The Examiner asserts that it would have been obvious to the skilled artisan to "incorporate the representation taught by Herzyk et al. with the method of Dahiyat et al. to gain the benefit of using less computer time for generating a single structure."

With regard to claims 6-8, the Examiner states that neither Dahiyat et al. nor Herzyk et al. teaches that the solvent is substantially water, but that it would have been obvious to the skilled artisan "to combine the teaching of Dahiyat et al., Herzyk et al. and those of Hurley et al." as Hurley et al. teach that "it would have been obvious to determine the structure of an amino acid in water because it would have allowed for the calculation of stability."

In view of the following these rejections are respectfully traversed.

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, as the U.S. Supreme Court very recently held in *KSR International Co. v. Teleflex Inc. et al.*, Slip Opinion No. 04–1350, 550 U. S. ____ (April 30, 2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of

ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (*KSR*, *supra*, slip opinion at 13-15.) Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

With regard to motivation to combine references, **MPEP 2143** discusses the requirements of a *prima facie* case of obviousness. First, there must be some suggestion or motivation to combine the reference teachings or to modify the reference, and second, there must be a reasonable expectation of success. Finally, the prior art reference or references when properly combined, must teach or suggest all the claim limitations.

Regarding motivation to modify properly combined references, **MPEP 2143.01** states that a proposed modification cannot render the prior art unsatisfactory for its intended purpose. If it does, then there is no suggestion or motivation to make the proposed modification. Further, the proposed modification cannot change the principle operation of a reference.

Regarding *teaching away*, **MPEP 2141.02** states that prior art must be considered in its entirety, including disclosures that *teach away* from the claims. See also **MPEP 2145(X)(D)**. The Federal Circuit in *Takeda v. Alphapharm* found that the prior art taught away from the closest compound because the prior art in fact disclosed a broad selection

of compounds where the closest prior art compound exhibited negative properties that would have led the skilled artisan away from that compound.

In *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.,* Federal Circuit, No. 06-1325 (June 28, 2007), the Federal Circuit rejected Alphapharm's argument that the prior art would have led one of ordinary skill in the art to select compound b as a lead compound most promising to modify in order to improve its antidiabetic activity and thus potentially arrive at the claimed pioglitazone. The district court considered three references in reaching its determination, namely Takeda's '200 patent; Sodha II; and Takeda's '779 patent. The district court found that Sodha II taught away from compound b and that any suggestion in the '779 patent to select compound b was essentially negated by the disclosure of Sodha II in view of the more exhaustive and reliable scientific analysis presented by Sodha II and the teaching away. Accordingly, the Federal Circuit accorded more weight to the Sodha II reference.

It is submitted that a *prima facie* case of obviousness has not been established.

In the response to the previous office action, claim 1 was amended to recite that a single sphere is used to represent the backbone of each amino acid and one to three additional spheres are used to represent the amino acid's side chain. In the present office action, the Examiner asserts that since this manner of representing an amino acid is disclosed in the Herzyk et al. publication, it would have been obvious to use this amino acid representation in the method of the Dahiyat et al. publication "to gain the benefit of using less computer time for generating a single structure." However, reducing computer time is not a goal in and of itself. The challenge is to reduce computer time ***without*** eliminating all candidate high resolution structures that are satisfactory solutions to the problem.

In the office action, the Examiner refers to the method of the Dahiyat et al. publication as "the computationally intensive method of Dahiyat." However, the method of the Dahiyat et al. publication ***is not*** "computationally intensive." Although the Dahiyat et al. publication uses an "all atom" representation of the amino acids, the Dahiyat et al. publication ***reduces*** computer time by implementing a search method based upon the ***dead-end elimination theorem*** (*see* abstract of Dahiyat et al.). Thus, Dahiyat et al. reduces computer time by a method that is ***completely different*** from the presently claimed method. Replacing the all atom representation of the Dahiyat et al. publication with the reduced representation of the Herzyk et al. publication would not produce the method of the present invention ***because the search method of the present application does not utilize the dead-end elimination algorithm***.

It is not possible to predict from the teachings of the Herzyk et al. publication whether or not, in any application of the described reduced amino acid representation, the most satisfactory solutions are eliminated. The inventors have found that using a reduced representation of the amino acids in their method does, in fact, yield a satisfactory ***high resolution*** protein structure. This could not have been predicted from the teachings of the Herzyk et al. publication. Quite to the contrary, the Herzyk et al. publication states at the end of the abstract : "The new representation is adequate for describing the 'low-resolution' features of protein structure such as the general fold and the positions of secondary structure elements. It can also provide an initial structure for more detailed refinement with the full all-atom representation." The skilled artisan reading the Herzyk et al. publication would understand that using the described manner of representing amino acids in the method of Dahiyat et al. would yield ***only a low resolution structure***, and that additional

work, i.e., full all-atom representation, would be required to produce a high resolution structure. The inventors have found, quite surprisingly, that the presently claimed method using a reduced representation of the amino acids, yielded a high resolution structure without any further refinement.

Accordingly, it is submitted that nothing in any of Dahiyat et al. and Herzyk et al., as well as Dahiyat et al., Herzyk et al. and Hurley et al., taken alone or together, renders the claimed subject matter obvious within the meaning of 35 USC §103. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

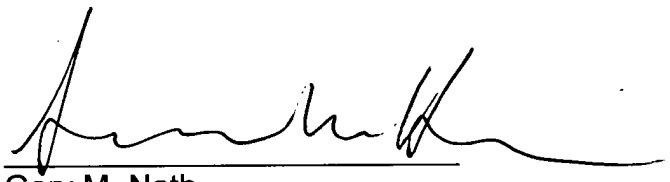
Conclusion

In view of the foregoing, Applicants submit that the application is in condition for immediate allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to contact the undersigned attorney if it is believed that such contact will expedite the prosecution of the application.

In the event this paper is not timely filed, Applicants petition for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

THE NATH LAW GROUP



Gary M. Nath
Registration No. 26,965
Susanne M. Hopkins
Registration No. 33,247
Customer No. 20259

Date: January 14, 2008
THE NATH LAW GROUP
112 South West Street
Alexandria, VA 22314
Tel: (703) 548-NATH
Fax: (703) 683-8396